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EXAMINER	
TURNER, SHARON L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,932	WU ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The amendment filed 4-4-05 has been entered into the record and has been fully considered.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn.

4. Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are pending.

Election/Restrictions

5. As previously of record, the claims are generic to a plurality of disclosed patentably distinct species comprising antibodies or antibody fragments that inhibit binding of chemokines a) MIP-1α, b) MIP-1β or c) RANTES to the human CCR5 receptor. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species of chemokine, i.e., either a) MIP-1α, b) MIP-1β or c) RANTES, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

This requirement is deemed necessary for examination purposes due to the introduction of the new limitations directed toward the specificity of the antibodies and antibody fragments to the different chemokines and arguments of record that the various chemokines are subject to different specific receptor binding parameters and hence the antibodies and antigen binding fragments thereof provide for different regional antibody binding/inhibiting specificity.

Applicant's election with traverse of RANTES in the reply filed on 7-19-04 is acknowledged. The traversal is on the ground(s) that the claims are drawn to antibodies and antibody fragments that bind CCR5 and not the different chemokines, that no arguments have been made that state the chemokines are subject to different specific receptor binding parameters or binding/inhibiting specificity, that the chemokine limitations are not new limitations and were previously searched and considered by the Examiner.

These arguments have been fully considered and are found to be persuasive. The restriction requirement is therefore withdrawn and claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are pending and are under examination. However, Applicant's are put on notice that distinction of the antibodies with respect to binding specificity may require reinstatement of the restriction (species) election requirement.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,528,625. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are rendered obvious in view of the '625 patented claims directed to the HB-12366 (2D7) antibody, antigen binding fragment, antibody producing hybridoma, compositions and test kit with properties including all limitations as instantly recited. The disclosure of the species renders obvious the instant generic recitations.

Applicants assert that a terminal disclaimer has been filed.

Applicant's assertion has been fully considered but is not persuasive. No terminal disclaimer was found within the submission of 4-4-05 or previous. Accordingly, rejection is maintained.

Priority

8. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

As set forth in the new matter rejection below, claims 147-210 are directed to a subgenus of antibodies not supported by the specification or within the noted priority documents as originally filed. In the amendment of 2-4-04, Applicants state that no new matter is added and that support for the newly recited claims may be found within the specification at p. 11, lines 18-19; p. 12, lines 1-2; and page 59, line 24 through page 60, line 23. However, particular support for the new claim recitations is not found at these cited passages. Support is noted for antibodies as directed at p. 11-12, paragraph spanning. Further, support is noted for 5C7 as at p. 60. However, the claims are not directed to the genus of antibodies contemplated/supported in the specification as originally filed.

In particular, the claims are directed to a subgenus of CCR5 antibodies which binds "*human* CCR5" wherein the antibody or fragment is further capable of inhibiting binding of *chemokines* (MIP-1α, MIP-1β and RANTES) *or combination thereof*, to human CCR5 and which *inhibits one or more functions associated with binding of a chemokine to the receptor.*" Yet these limitations differ from the disclosure as directed at p. 11-12, to antibodies or antigen binding fragments that inhibit binding of a "*ligand*"

and "*one or more functions mediated by CCR5 in response to the ligand.*" Moreover, specific support for the further subgenus of these antibodies that are chimeric, human, humanized, binds the second extracelluar loop and inhibits HIV infection are not specifically noted.

Therefore the effective filing date with respect to instant claims is the instant filing date of May 30, 2001. Traversal of the priority determination should note where all claim limitations are specifically supported within Applicant's specification and the noted priority documents for the earliest effective filing date sought.

Applicants argue as extensively set forth in the 4-4-05 response, pp. 12-15, particularly noting the Table at pp. 14. Newly amended claims are particularly directed to antibodies or antigen binding fragments thereof which bind to the second extracellular loop of a human chemokine receptor 5 (CCR5)..., as claimed. As noted, in the Table at p. 14 of the response, support is not found for such recitations prior to the disclosure of 6,528,625, filed July 11, 1997. Accordingly instant claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 may only obtain the benefit of the **7-11-1997** date.

Claim Objections

9. Claims 148, 159, 169, 180, 190, 201 and 204 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims do not further limit the parent or independent claims

because the parent or independent claims already specify that the antibody or antigen binding fragment binds/has specificity for human chemokine receptor 5.

Applicants argue as set forth in the 4-4-05 response at p. 15, particularly that claims directed to "specificity" further limit in that not all antibodies that bind to an antigen are necessarily specific for only that antigen.

Applicant's arguments filed 4-4-05 with respect to "specificity" have been fully considered but are not persuasive, in particular absent some identifying characteristic that delineates the difference in scope of the claim, ie., an indication of how the artisan may ascertain those antibodies that have "specificity" from those that "bind." Note that the new 112, second paragraph rejection on this ground is as necessitated by Applicant's arguments presented in this amendment.

Claim Rejections - 35 USC § 101

10. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims do not reflect isolation, or the hand of man and read on a naturally produced product of nature. The term 'isolated' should be inserted so as to recite "An isolated antibody or antigen binding fragment thereof...".

Applicants argue in the 4-4-05 response the claims as directed to compositions and kits distinguish *inter alia* that the antibody is isolated.

Applicants arguments filed 4-4-05 have been fully considered but are not persuasive considering naturally occurring antibodies or antigen binding fragments that are generated in vivo and exist in bodily fluids, for example.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies or antigen binding fragments thereof that inhibit binding of chemokine ligands MIP-1α, MIP-1β and RANTES to human CCR5, and for the specific deposits of antibodies 5C7 and 2D7 as noted in the deposits; does not reasonably provide enablement for antibodies with such functional recitations specific to chemokine binding, functions associated with binding of a chemokine to the receptor to antibodies or to specific epitope regions such as the second extracellular loop. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The grounds of rejection are as set forth in the Office action of Paper No. 14, 4/15/03 and are as set forth herein with respect to the amended claims. Amendment to "human CCR5" has obviated the grounds of rejection with respect to the recitation of any "mammalian" CCR5. However, the aforementioned claims remain drawn

generically to any chemokine capable of binding human CCR5. As previously set forth, only chemokines MIP-1α, MIP-1β and RANTES are disclosed as binding human CCR5.

Further, as to the new recitations directed to "inhibit(ing) HIV infection," the specification teaches that specific monoclonal antibodies with epitope specificity within the region of the amino terminus or second extracellular loop were capable of inhibiting binding and entry of HIV, see in particular pp. 60-67, especially pp. 65-67. In contrast, only antibodies with epitopes specific to the second extracellular loop were capable of inhibiting binding of chemokines MIP-1α, MIP-1β and RANTES to human CCR5.

Instant claims are directed generically to antibodies or antigen binding fragments that bind to human CCR5 and inhibit binding of a chemokine to the receptor, inhibits one or more functions associated with binding of the chemokine to the receptor and inhibits HIV infection. Accordingly, Applicants have chosen to define the antibodies and antigen binding fragments solely by functional properties of the 2D7 species. While an antibody molecule imparts some particular structure, for example heavy and light chains, the epitope specificity of the antibody and binding properties are directed by the antibody structure within the variable binding domain of the molecule. However, only the 2D7 antibody with epitope specificity within the second extracelluar loop is disclosed as exhibiting the claimed characteristics, i.e., for inhibition of chemokines MIP-1α, MIP-1β, RANTES and HIV binding as well as inhibition of one or more functions associated with binding of the chemokine to the receptor and inhibition of HIV entry.

Yet the claims do not delineate these apparent structural constraints of the antibody variable domains. Further the claims fail to recite the epitope specificity

apparently required for conveying these properties, i.e., specificity for the second extracellular loop. No other structural, functional or epitope specificity guidance is provided. Thus, absent further direction, the artisan cannot make and use the antibodies with the recited functional properties without further undue experimentation to define those portions conveying the functional constraints and/or further characterization of any other epitopes capable of sharing the recited functional characteristics.

Finally, the Examiner notes that Applicant's arguments in traverse of the art rejections of record support the aforementioned scope of enablement rejection. In particular, applicants argue for example that Olson supports that not all antibodies have the function of inhibiting chemokine binding and one or more functions associated with chemokine binding. To the extent that applicants argue the prior art as non-enabling, so to does Olson support non-enablement within the full scope of the claims absent specific guidance as to those structural and functional characteristics of a genus of antibodies capable of providing the recited functions.

It is noted that the specifics of the deposit are enabled as set forth in the preamble of this rejection. However, the claims depend from a rejected base claim and thus are rejected herein as being dependent thereon. To the extent that the deposits refer to a preamble that is not fully enabled and does not suitably describe the deposits, rejection is maintained over the accession numbers. While applicants may not rewrite the claims with all limitations of the independent claim to expedite allowance, Applicants

may rewrite an independent claim directed to the deposits or rewrite the preamble such that it is in scope with the disclosure.

Thus in view of the extensive breadth of the instant claims, the presence of working examples that are limited to a single antibody 2D7 capable of inhibiting binding of the three known chemokine ligands of human CCR5, the unpredictability associated with identifying other chemokines that bind human CCR5 with the required functional constraints and the absence of guidance as to the generic characteristics of such antibodies and epitope specificity for the second extracellular loop including for HIV binding and entry; the experimentation left to those skilled in the art to make and use the antibodies as currently broadly recited is unnecessarily, and improperly, extensive and-undue. The rejection is maintained for the reasons of record set forth in full in Paper No. 14 and as further noted herein.

Applicants argue in the 4-4-05 response as extensively set forth at pp. 17-19 that the claim amendments obviate rejection and that the basis for rejection with respect to a single means claim (MPEP 2164.08) is unclear.

Applicant's arguments filed 4-4-05 have been fully considered but are not fully persuasive for the following reasons. It is acknowledged that the claims as set forth are fairly represented via the single species of monoclonal antibody disclosed as 2D7 and as Accession No. HB-12366. In particular, this antibody is noted to bind to the second extracellular loop of human CCR5, inhibits binding of chemokines MIP-1α, MIP-1β and Rantes and inhibits HIV entry as noted in the Examples and Figures. However, this antibody is a single species member of a genus of antibodies and antigen binding

fragments thereof as claimed. The antibody was made as disclosed at pp. 58 of the specification. As noted therein, the antibody was formed, "by immunizing mice with L1.2 cells expressing high levels of transfected CCR5-F1ag, as described (Wu et al., J Exp. Med., 285:1681-1691 (1997))." This is the same procedure denoted for the dissimilar antibody isolate of 5C7 noted to differ from 2D7 in epitope specificity. In particular 5C7 and 3A9 are specific to the amino terminal of CCR5 while 2D7 is specific to the 2nd extracellular loop. Thus, this experimental data evidences the unpredictable nature of determining antibody/antigen epitope specificity for any given antigen antibody combination. Experimental research may be the only way to distinguish difference. In response to the art rejections noted below, Applicant's continue arguments that the prior art is not enabling in that specific structural characteristics correlating with the noted functional recitations of the claims are not prescribed. Applicants specification establishes the principle that the chemokine binding site of MIP-1α, MIP-1β and Rantes is within the 2nd extracellular loop of human CCR5 and that this portion is also responsible for the additionally recited property of inhibiting HIV entry. To the extent that Applicant argues the prior art rejections noting that the ability of an antibody to inhibit binding of any one of the noted chemokines fails to denote the particulars for any other chemokine or inhibition of HIV entry, so to does the instant specification appear to be defective for such would indicate a critical element for distinguishing the functional properties amongst the second extracellular loop or portions of the second extracellular loop. In that case, the Examiner cannot ascertain that which Applicant has contributed over the prior art, particularly as the prior art acknowledges the importance of the

second extracellular loop in ligand binding and inhibition of HIV infection. To the extent that Applicants maintain the prior art as non-enabling, the Examiner maintains the enablement rejection absent definitive analysis or evidence which clarifies the aforementioned inconsistencies. To clarify, the Examiner has not confused the instant claims with a single means claim (means plus function claim). Nevertheless, the claims are akin or analogous in the sense that the recitations are of a functional variety where only a single structural species is disclosed (2D7). It is not apparent that the single species is fully representative of the genus claim, or that it provides the artisan with the ability to make and/or use the other structural elements (antibodies or antigen binding fragments thereof) that correlate to the functional recitations of the claims. Rejection on these grounds is therefore maintained pending resolution of the applicability of the prior art.

14. Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The grounds of rejection are as set forth in the Office action of Paper No. 14, 4/15/03 and as set forth herein with respect to the claim amendments. Amendment to "human CCR5" has obviated the grounds of rejection with respect to the recitation of any "mammalian" CCR5. However, the aforementioned claims are drawn generically to

any chemokine capable of binding human CCR5 and inhibiting one or more functions associated with binding of the chemokine to the receptor, to the second extracellular loop and to inhbiting HIV infection. As previously set forth, only chemokines MIP-1α, MIP-1β and RANTES are disclosed as binding human CCR5.

Applicants argue in the response of 7-19-04 that disclosure of MIP-1α, MIP-1β and RANTES binding to human CCR5 constitutes a sufficient number of species to meet the written description requirement.

Applicants arguments filed 7-19-04 have been fully considered but are not persuasive. As previously noted, while the Examiner acknowledges that the CC chemokine family shares some common structural motifs, the evidence of record establishes that this shared family structure does not convey the functional activities of CCR5 specific binding since not all CC chemokines (as identified) bind CCR5. In addition, it is again noted that the instant claims encompass antibodies that inhibit binding of any chemokine to human CCR5 and any one or more functions associated with binding. Applicants have not described what structural attributes make any chemokine capable of binding human CCR5 or what functions are associated. Nor have they provided the artisan with any means to immediately envision or predict from all chemokines, those which would be capable of binding human CCR5 and exhibiting the noted functional characteristics. Absent a sufficient description of the receptor-ligand pairs, or a means for immediately recognizing those chemokines that readily bind, there is not adequate written description support of the genus as directed to antibodies or antigen binding fragments that inhibit binding of any chemokine to the

human CCR5 receptor and further that provides for inhibition of one or more ill described functions associated with binding of the chemokines to the receptor.

Moreover, the specification teaches the apparent requirement for the antibody or antigen binding fragment to be specific to the second extracellular loop in order for the antibodies to provide the noted functional characteristics, yet such is not an element of the claims, nor is there sufficient support to denote that this division is a further sub-species or sub-genus readily contemplated by Applicnats.

Further, as to the new recitations directed to "inhibit(ing) HIV infection," the specification teaches that monoclonal antibodies to the amino terminus or second extracellular loop were capable of inhibiting HIV binding and entry, see in particular pp. 60-67, especially pp. 65-67. In contrast, only antibodies to the second extracellular loop of CCR5 were capable of inhibiting binding of chemokines MIP-1α, MIP-1β and RANTES to human CCR5 and inhibiting HIV binding and entry. These specifics are not limitations of the claims.

Accordingly, Applicants have chosen to define the antibodies and antigen binding fragments solely by functional characteristics without structural requirements that direct those characteristics. While an antibody molecule imparts some particular structure, for example heavy and light chains, the specificity of antibody binding is dependent upon the structure of the variable domain of the antibody molecule. Only antibodies with specificity to the second extracelluar loop are disclosed as exhibiting the claimed characteristics, i.e., for inhibition of chemokines MIP-1α, MIP-1β, RANTES and HIV binding as well as HIV entry.

Yet the claims do not delineate these apparent structural constraints of the antibody variable domains. Further the claims fail to recite the epitope specificity apparently required for conveying these properties, i.e., specificity for the second extracellular loop. No other structural, functional or epitope specificity guidance is provided. Without such description the artisan cannot immediately envisage those antibodies capable of meeting the claim recitations and adequate written description support is not provided for a genus.

Finally, the Examiner notes that Applicant's arguments in traverse of the art rejections of record support the aforementioned written description rejection. In particular, Applicants argue that Olson evidences that not all antibodies have the function of inhibiting chemokine binding and one or more functions associated with chemokine binding. To the extent that applicants argue the prior art as not-sufficiently described (for lacking particular description of the properties), so to is Applicant's specification lacking in description of those specific structural characteristics providing for the recited functional constraints. Thus, the rejection is maintained for the same reasons of record as set forth in the Office Action of 4/15/04, Paper No. 14 and as noted herein.

Applicants argue in the 4-4-05 response at pp. 20 that the claim amendments obviate rejection.

Applicant's arguments filed 4-4-05 have been fully considered but are not fully persuasive for the following reasons. It is acknowledged that the claims as set forth are fairly represented via the single species of monoclonal antibody disclosed as 2D7 and

as Accession No. HB-12366. In particular, this antibody is noted to bind to the second extracellular loop of human CCR5, inhibits binding of chemokines MIP-1α, MIP-1β and Rantes and inhibits HIV entry as noted in the Examples and Figures. However, this antibody is a single species member of the genus of antibodies and antigen binding fragments thereof as claimed. The antibody was made as disclosed at pp. 58 of the specification. As noted therein, the antibody was formed, "by immunizing mice with L1.2 cells expressing high levels of transfected CCR5-F1ag, as described (Wu et al., J Exp. Med., 285:1681-1691 (1997))." This is the same procedure denoted for the dissimilar antibody isolate of 5C7 noted to differ from 2D7 in epitope specificity. In particular 5C7 and 3A9 are specific to the amino terminal of CCR5 while 2D7 is specific to the 2nd extracellular loop. Thus, this experimental data evidences the unpredictable nature of determining antibody/antigen epitope specificity for any given antigen antibody combination. Experimental research may be the only way to distinguish difference. In response to the art rejections noted below, Applicant's continue arguments that the prior art is not enabling in that specific structural characteristics correlating with the noted functional recitations of the claims are not prescribed. Moreover, Applicants maintain that selection for example based on HIV inhibition would not necessarily lead to antibodies specific to the 2nd extracellular loop and which inhibit binding of the noted chemokines MIP-1α, MIP-1β and Rantes. Applicants specification establishes the principle that the chemokine binding site of MIP-1α, MIP-1β and Rantes is within the 2nd extracellular loop of human CCR5 and that this portion of CCR5 is also responsible for the additionally recited property of inhibiting HIV entry. Yet the prior art teaches

selection of antibodies based on the aforementioned criteria, for example to inhibit ligand binding, function of the receptor, inhibiton or HIV entry and specifically guides to the 2nd extracellular loop for these properties, see for example art of record. To the extent that Applicant argues the prior art rejections noting that the ability of an antibody to inhibit binding of anyone of the noted chemokines fails to denote the particulars for any other chemokine or inhibition of HIV entry, so to does the instant specification appear to be defective for such would indicate a critical element for distinguishing the functional properties required more than the simple screens exemplified within the prior art and Applicant's specification. In this case, the Examiner cannot ascertain that which Applicant has contributed over the prior art, or which argument is more correct, that the prior art is non-enabled but the specification is. To the extent that Applicants maintain the prior art as non-enabling, the Examiner maintains the enablement rejection absent definitive analysis or evidence which clarifies the aforementioned inconsistencies. With respect to written description, the claim recitations directed to antibodies or antigen binding fragments thereof, the antibodies and fragments are not delineated structurally but instead by their functional characteristics in binding the 2nd extracellular loop, inhibiting chemokine binding or HIV entry where only a single structural species (2D7) is disclosed. It is not apparent that the single species is fully representative of the genus claim, or that it provides the artisan with the means to make and/or use the other structural elements that correlate to the functional recitations. Rejection on these grounds is therefore maintained.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are rejected under 35 U.S.C. 102 (e) as being anticipated by Li et al. (US Pat. No. 6,025,154, Feb. 15, 2000, IDS AE, see entire document) as evidenced by Wu et al. (J. Exp. Med. 1997; 186(8): 1373-1381, October, IDS #AS4), Samson et al., J. Biol Chem., Oct. 1997, 272(40):24934-41, Raport et al., 1996 IDS Reference AW and Combadiere et al., 1996 IDS Reference AT3, and Atchison, IDS Reference AZ5. The grounds of rejection are as set forth in the Office Action of 1/10/03, Paper No. 14 and as further set forth herein.

Applicants argue in the response of 7-19-04 that the Li reference is not sufficiently enabled or described because the reference does not disclose any CCR5 ligands, does not exemplify the screening assays or actually make the antibodies. Applicants further argue that the limitations of the claims are not necessarily provided within the disclosure of Li. Further Wu is said not to supplement in that it does not establish that the Li antibodies would necessarily inhibit binding of one or more functions of the chemokines of CCR5 (MIP-1α, MIP-1β and RANTES) with reference to

Olson. Applicants thus submit that the recitations of specific chemokines and binding to the second extracellular loop teach over the prior art.

Applicants arguments have been fully considered but are not persuasive. As previously noted, Olson unlike Li, did not select for antagonists (antibodies) inhibiting chemokine binding but rather antibodies that blocked HIV mediated fusion, see in particular p. 4147. Such identified antibodies were subsequently tested for their effect on chemokine binding. Thus, Olson is directed to a different screen and does not teach away from the screening taught by Li. The selection of chemokines MIP-1α, MIP-1β and RANTES that bind CCR5 is not an inventive contribution as suggested by applicants. Such ligands were already recognized as ligands binding CCR5 and mediating receptor signaling, see in particular Raport et al., 1996 IDS Reference AW and Combadiere et al., 1996 IDS Reference AT3, for example. The Li reference teaches to screen for antibodies that inhibit chemokine binding and the functions of chemokine binding at the receptor. Thus, the Li reference does teach and is enabling for the screening of the specifically known ligands as well as their receptor functions as established in the art. Moreover, Raport notes that, "this same combination of chemokines has recently been shown to potently inhibit human immunodeficiency virus replication in human peripheral blood leukocytes," and others citing the N-terminus and second extracellular loop as important in mediating HIV infection, and in part separable from chemokine binding (with reference to the N-terminus), see in particular Atchison, IDS Reference AZ5. Further, that the Li chemokine binding region is within the second extracellular loop is established as via Wu, and moreover via Samson, J. Biol Chem.,

Oct. 1997, 272(40):24934-41, now of record. Accordingly, the screening assay of Li would necessarily result in the identification of antibodies specific to the second extracellular loop, i.e., the chemokine binding and signaling site. That this site is also evidenced as the major co-receptor allowing infection of HIV is further evidenced as noted via Samson and Atchison. Hence, the screening assay of Li would further necessarily identify antibodies capable of inhibiting infection of HIV as the ligand binding site of the second extracellular loop is critical to HIV infection. Both properties are evidenced as mapping to the same site, i.e., within the second extracellular loop, see in particular Wu, Atchison, Samson, Raport and Combardiere. To the extent that the parent claims are rejected, so to must the noted deposit absent identifying characteristics that would teach over the prior art. Thus, the rejection is maintained with further evidence as to the newly directed functional properties.

Applicants argue in the 4-4-05 response as extensively set forth at pp. 21-27 of the response. In particular, Applicants argue that Li is not enabled as it does not disclose any chemokine CCR5 ligand, that the specific ligand were not disclosed until after the patents filing date, that no such assays were disclosed and that no recognition of HIV inhibiton of infection, binding or entry was noted. Applicants further argue that the reference cannot anticipate as it does not teach each and every element of the claims. Applicants further point to the Declaration of Walter Newman noting that not all antibodies to CCR5 necessarily have the noted functional properties as claimed. Applicants further assert that inherency is not established as there is no basis for reasoning that the elements are necessarily provided.

Applicants arguments filed 4-4-05 have been fully considered but are not persuasive. The Li patent clearly teaches antibodies capable of inhibiting chemotaxis, a function of chemokine binding at the CCR5 receptor, that inhibit ligand binding and receptor function, see in particular, column 2, lines 65-67, columns 11-12. Further the patent denotes the transmembrane structure of the GPCR, particularly of extracellular portions, denotes soluble forms of the receptor that are the extracellular portions separate from the cytoplasmic and transmembrane domains and antibodies to such fragments or portions.

Detailed Description Text (9):

"The polynucleotides may also encode for a soluble form of the G-protein chemokine receptor polypeptide which is the extracellular portion of the polypeptide which has been cleaved from the TM and intracellular domain of the full-length polypeptide of the present invention."

Detailed Description Text (98):

The polypeptides, their fragments or other derivatives, or analogs thereof, or cells expressing them can be used as an immunogen to produce antibodies thereto. These antibodies can be, for example, polyclonal or monoclonal antibodies. The present invention also includes chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of an Fab expression library. Various procedures known in the art may be used for the production of such antibodies and fragments.

Detailed Description Text (99):

Antibodies generated against the polypeptides corresponding to a sequence of the

present invention can be obtained by direct injection of the polypeptides into an animal or by administering the polypeptides to an animal, preferably a nonhuman. The antibody so obtained will then bind the polypeptides itself. In this manner, even a sequence encoding only a fragment of the polypeptides can be used to generate antibodies binding the whole native polypeptides. Such antibodies can then be used to isolate the polypeptide from tissue expressing that polypeptide.

Accordingly the patent fairly teaches antibodies to such extracellular portions. Screening on the basis of antibodies reactive to extracellular portions would necessarily result in the selection of antibodies specific to the second extracellular portion and this is the same portion corresponding to the second extracellular loop, that is evidenced to bind the chemokines, mediate chemotaxis and mediate HIV entry. Accordingly, Li fairly teaches the identification of antibodies exhibiting the delimited functional recitations absent evidence to the contrary. Antibodies to the extracellular portion(s) possess such properties. Li receives priority to June 6, 1995, prior to the awarded effective filing date of 7-11-97.

17. Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are rejected under 35 U.S.C. 102(e) as being anticipated by Hoxie (US Pat No. 5,994,515, Nov. 30, 1999, IDS AB, see entire document) as evidenced by Olson et al..(J. Virol., 1999; 73:4145-4151, IDS #AW5) and Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4). The grounds of rejection are as set forth in the Office Action of 1/10/03, Paper No. 14 and as further reiterated herein.

Applicants argue in the response of 7-19-04 that Hoxie does not necessarily provide the recited antibodies or teach the noted limitations. Applicants argue that Hoxie's experimentation is to CXCR4 and not CCR5. In particular, Applicant's position is that the antiviral antibodies of Hoxie would not necessarily exhibit the inhibition of chemokine binding or one or more functions associated with binding. Applicants point to the teachings of Atchison and Gosling as to partially dissociable activities within CCR5 for HIV infection and chemokine signaling. Applicants assert that the Olson teachings do not mean that an antibody that inhibits HIV entry as disclosed by Hoxie would necessarily have the properties of instant claims.

Applicant's arguments filed 7-19-04 have been fully considered but are not persuasive. Hoxie's method includes screening for antibodies capable of inhibiting HIV infection. Olson notes the most effective antibodies identified via such selection criteria are those that bind at the second extracellular loop, within the chemokine ligand binding domain and which inhibit calcium flux (receptor function). Thus, while it is true that other antibodies may be identified using the inhibition of envelope fusion and entry as selection criteria. Nevertheless, Olson evidences that the clamed antibodies are necessarily provided using such screening techniques as the antibodies were subsequently identified as antibodies capable of inhibiting HIV infection, inhibiting chemokine binding and receptor function. In particular, the antibodies that are the most effective at inhibiting HIV infection and are necessarily selected based upon this selection criteria, are noted to be specific to the ligand binding site and to inhibit calcium influx (receptor function). The reference is fully enabled for that selection criteria for

which it teaches and the human CCR5 antibodies that share these characteristics. To the extent that the parent claims are rejected, so to must the noted deposit absent identifying characteristics that would teach over the prior art. Thus, rejection is maintained.

Applicants argue in the 4-4-05 response that Hoxie does not teach each and every element of the claims, that of the antibodies produced some did not correlate to the properties of the claims, and that Hoxie does not teach the correlation of the noted functional elements. Applicants argue that Olson and Wu are not supportive to the missing elements or evidence that the properties are necessarily provided. Applicant's arguments filed 4-4-05 have been fully considered but are not persuasive. As noted above Hoxie directs to the second extracellular domain (loop) and to antibodies to this second extracellular domain (loop). The properties of this portion are particular noted and evidenced as chemokine binding and inhibition of HIV entry. That the antibodies are so specific, necessarily provides the correlated functional properties. An old product does not become new upon identification of a new property. Hoxie's silence to the correlation of the functional properties is of no concern. The antibodies are specific to the same second extracellular loop and hence necessarily share the same functional properties absent evidence to the contrary. Nevertheless Hoxie further notes the functional inhibition of HIV entry and inhibition of calcium flux mediated via receptor function. Hoxie receives priority to June 27, 1996, prior to the awarded effective filing date of 7-11-97.

18. Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are rejected under 35 U.S.C. 102(b) and 102(e) as being anticipated by Littman et al. (US Pat. 5,939,320, Aug. 17, 1999, IDS # AA, see entire document) as evidenced by Olson et al., (J. Virol., 1999; 73:4145-4155, IDS.#AW5) and Wu et al. (J. Exp. Med. 1997; 186(8):1373-1381, IDS #AS4). The grounds of rejection are as set forth in the Office Action of 1/10/03, Paper No. 14 and as further reiterated herein.

Applicants argue in the response of 7-19-04 essentially as noted above, that Littman does not necessarily provide the recited antibodies or teach the noted limitations of the claims as to chemokine binding and receptor function. In particular, Applicant's position is that the antiviral antibodies of Littman would not necessarily exhibit the inhibiton of chemokine binding or one or more functions associated with binding. Applicants assert that the Wu and Olson teachings do not mean that an antibody that inhibits HIV entry as disclosed by Littman would necessarily have the properties of instant claims.

Applicant's arguments filed 7-19-04 have been fully considered but are not persuasive. Littman's method is for screening for antibodies capable of inhibiting HIV infection. Olson notes the most effective antibodies identified via such selection are those that bind at the second extracellular loop, within the chemokine ligand binding domain and which inhibit calcium flux (receptor function). Thus, while it is true that other antibodies may have been identified using such selection criteria, nevertheless, Olson evidences that the antibodies recited are necessarily provided. In particular,

these are the antibodies that are the most effective at inhibiting HIV infection and would necessarily be selected and identified based upon the noted selection criteria. To the extent that the parent claims are rejected, so to must the noted deposit absent identifying characteristics that would teach over the prior art. Thus, rejection is maintained.

Applicants argue in the 4-4-05 response that Littman does not teach each and every element of the claims, the correlation of chemokine binding and HIV entry to the second extracellular loop or that antibodies to the second extracellular domain are necessarily provided.

Applicants arguments filed 4-4-05 have been fully considered but are not persuasive. The selection criteria delineated is for inhibition of HIV entry. As evidenced above, while other portions of the receptor additionally correlate to HIV entry, the method would nevertheless necessarily identify antibodies specific to the second extracellular loop because the second extracellular loop is a specific portion evidenced to mediate entry. An old product does not become new based upon the identification of new properties. Littman receives priority to 5-20-1996, prior to the awarded effective filing date of 7-11-97. Accordingly, rejection is maintained.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chuntharapai et al. (US Pat. No. 5,543,503, IDS Ref. AD) in view of either Rapport et al J. Biol. Chem. 271:11161.17166 1996, IDS Ref. AW), Samson et al. (Biochem. 35:3362-3367 1996, IDS Ref. AV), or Combadiere et. al. (J. Leukoc.,Biöl. 60:147-152 1996, IDS Ref. AT)), as evidenced by Wu et al. (J. Exp. Med. 1997; 186(8):1373.-1381, IDS Ref. AS4). The grounds of rejection are as set forth in the Office Action of 1/10/03, Paper No. 14 and as further reiterated herein.

Applicants argue in the response of 7-19-04 that the prior art does not provide the suggestion or establish reasonable expectation of success. Applicants submit that the combination fails to teach an anti-CCR5 antibody which inhibits chemokine binding and inhibition of receptor function. Applicants argue that the prior art is not directed to the same antibodies claimed and that the declaration of Walter Newman as to the difficulty in obtaining antibodies to CCR5 establishes no expectation of success.

Applicants arguments filed 7-19-04 have been fully considered but are not persuasive as Chuntharapai notes the suggestion of making antibodies specific for a chemokine family receptor such that the antibodies bind and inhibit receptor function. The human CCR5 receptor and chemokine ligands were known in the art as well as suitable assays for assessing binding and receptor function. The suggestion and means for screening are suitably provided and the making of such antibodies, while requiring extensive experimentation does not involve experimentation that is undue or

not well established in the art. Thus, both suggestion and reasonable expectation of success are provided. To the extent that the parent claims are rejected, so to must the noted deposit absent identifying characteristics that would teach over the prior art. Thus, rejection is maintained.

Applicants argue in the 4-4-05 response as set forth at pp. 33-38. In particular Applicants argue that the combination does not arrive at the invention because it does not specifically teach or suggest an antibody having all of the characteristics of the claims. Applicants further argue no expectation of success for isolating specific antibodies that correlate to the claims.

Applicants arguments filed 4-4-05 have been fully considered but are not persuasive. In contrast to Applicants position that such screening for ligand binding and antibodies capable of inhibition such ligand binding, the Examiner finds such to be evidenced in the art as routine. The references are not required to teach the correlation of the multiple functions, merely that the references enable selection of antibodies that are inhibitory to ligand binding. As such is evidence to be routine as noted in Chuntharapai et al., for example, sufficient suggestion is provided as well as an expectation of success.

21. Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, 207-208 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chuntharapai et al. (US Pat. No. 5,543,503, IDS Ref. AD) in view of either Rapprt et al J. Biol. Chem. 271:11161.17166 1996, IDS Ref. AW), Samson et al. (Biochem. 35:3362-3367 1996, IDS Ref. AV), or

Combadiere et. al. (J. Leukoc.,Biöl. 60:147-152 1996, IDS Ref. AT)), as evidenced by Wu et al. (J. Exp. Med. 1997; 186(8):1373.-1381, IDS Ref. AS4) further in view of Ramakrishnan et al., (US Pat. No. 5,817,310). The grounds of rejection are as set forth in the Office Action of 1/10/03, Paper No. 14 and as further reiterated herein.

Applicants argue in the response of 7-19-04 that the prior art does not provide the suggestion or establish reasonable expectation of success. Applicants submit that the combination fails to teach an anti-CCR5 antibody which inhibits chemokine binding and inhibition of receptor function. Applicants argue that the prior art is not directed to the same antibodies claimed and that the declaration of Walter Newman as to the difficulty in obtaining antibodies to CCR5 establishes no expectation of success. Applicants further argue with respect to Ramakrishnan that the teachings as to chimeric or humanized antibodies fail to remedy the deficiencies of the aforementioned references.

Applicants arguments filed 7-19-04 have been fully considered but are not persuasive as Chuntharapai notes the suggestion of making antibodies specific for a chemokine family receptor such that the antibodies bind and inhibit receptor function. The human CCR5 receptor and chemokine ligands were known in the art as well as suitable assays for assessing binding and receptor function. The suggestion and means for screening are suitably provided and the making of such antibodies, while requiring extensive experimentation does not involve experimentation that is undue or not well established in the art. Thus, both suggestion and reasonable expectation of success are provided. Ramakrishnan further provides the suggestion and means for

making suitable chimeric and humnanized antibodies. The suggestion is provided as well as expectation of success. To the extent that the parent claims are rejected, so to must the noted deposit absent identifying characteristics that would teach over the prior art. Thus, rejection is maintained.

Applicants argue in the 4-4-05 response as extensively set forth at pp. 38-39. In particular Applicants maintain that the combination of references does not arrive at direction to chimeric antibodies of the claimed invention specific to inhibition of ligand binding.

Applicants arguments filed 4-4-05 have been fully considered but are not persuasive. Selection of antibodies that inhibit ligand binding enables the selection of antibodies to the second extracellular loop and which share the noted functional properties of the claims. Thus, the suggestion of providing human, chimeric, humanized or other host modified IgG is fairly suggested and provide. Rejection is maintained where no evidence contradicts.

Conclusion

22. No claims are allowed.

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

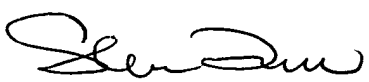
24. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

Sharon L. Turner, Ph.D.
June 22, 2005



SHARON TURNER, PH.D.
PRIMARY EXAMINER
6-22-05

Continuation of Disposition of Claims: Claims pending in the application are 147,148,150-153,155,156,158-163,165,166,168,169,171-174,176,177,179-184,186,187,189,190,192-195,197,198,200-205,207 and 208.